# Characterization of Cyclopentyllithium and Cyclopentyllithium Tetrahydrofuran Complex

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S *Supporting Information*

ABSTRACT: The solid-state structures of unsolvated, hexameric cyclopentyllithium and tetrameric cyclopentyllithium tetrahydrofuran solvate were determined by single-crystal X-ray diffraction. Cyclopentyllithium easily crystallized in hydrocarbon solvents. Solution-state structural analyses of cyclopentyllithium and cyclopentyllithium−tetrahydrofuran complexes in toluene-d_8 were also carried out by diffusion-ordered NMR spectroscopy with diffusion coefficient−formula weight correlation analyses and other one- and two-dimensional NMR techniques. The solution-state studies suggest that unsolvated cyclopentyllithium exists as hexamer and tetramer equilibrating with each other. Upon solvation with tetrahydrofuran, cyclopentyllithium exists mostly as a tetrahydrofuran tetrasolvated tetramer.
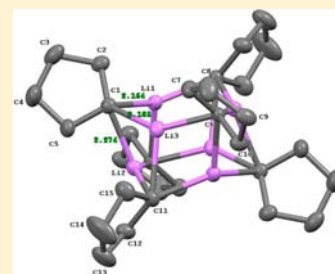
INTRODUCTION

Organolithium reagents are among the most widely used reagents in the synthesis of organic compounds.[1] Alkyllithium reagents are the source of most organolithium reagents because they can efficiently generate a wide variety of carbanions, such as lithium amide, acetylide, and alkoxide. Moreover, the low boiling point alkane byproduct is a saturated hydrocarbon that is inert to most of the reactions. Secondary alkyllithium reagents are usually used for the deprotonation of very weakly acidic protons, such as aryl and alkyllithium.[1,2] Although they are not as nucleophilic as primary alkyllithium reagents, secondary alkyllithium reagents can also be used as nucleophiles and used for metal−lithium exchange.[1,3] It is evident that the reactivity and preferred reaction pathways of these alkyllithium reagents are related to their aggregation and solvation states;[1,4] thus, any such information regarding these intermediate states can enhance our understanding and ability to tailor these reactions to the desired products. Herein we present the structural characterization in both solid and solution of cyclopentyllithium, a secondary alkyllithium reagent.

The deprotonation reactions of alkyllithium reagents are often carried out in the presence of ethereal solvents such as tetrahydrofuran (THF) and diethyl ether, to increase the reactivity of the reagents. However, it is well-known that alkyllithium reagents α-deprotonate ethereal solvents.[1,5] Therefore, it is not easy to obtain the crystal structure of alkyllithium adducts with tetrahydrofuran. The first crystal structures of *n*-butyllithium were reported 20 years ago, including the THF-solvated tetramer.[6] After that, only two structures of THF-solvated alkyllithium reagents have been published.[7] However, these two published structures are primary alkyllithium reagents, possibly because secondary alkyllithium reagents react more readily with THF. Because cyclopentyllithium crystallizes readily, we were also able to obtain the crystal structure of its complex with tetrahydrofuran. This is the first crystal structure of a secondary alkyllithium−THF complex,

although a few internally chelated and mixed aggregate secondary alkyl lithium containing structures are known.[8] Moreover, characterization of the cyclopentyllithium/THF complex in toluene-d_8 solution is also described using various one- and two-dimensional NMR techniques on the dissolved crystal.

RESULTS AND DISCUSSION

Part I. Characterization of Cyclopentyllithium in Solid and Solution States. Cyclopentyllithium is easily synthesized by reacting chlorocyclopentane with lithium in cyclohexane or heptane under argon atmosphere. Owing to the greater solubility of cyclopentyllithium in cyclohexane, yields were always greater than those obtained in heptane under otherwise analogous conditions.

Crystal Structure of Cyclopentyllithium. Cyclopentyllithium was easily crystallized in hydrocarbon solvents. When freshly made cyclopentyllithium cyclohexane solution or heptane solution is stored at −20 °C overnight, a significant amount of colorless cyclopentyllithium crystals is obtained and the concentration of cyclopentyllithium cyclohexane solution decreases from 2.0 to 0.6 M. Crystallization provides highly pure, crystalline secondary alkyllithium in good yield. The X-ray structure determination reveals that cyclopentyllithium is hexameric in the solid state (Figure 1) similar to *n*-butyllithium,[9a] isopropyllithium,[9b] and cyclohexyllithium.[9c]

Characterization of Cyclopentyllithium in Solution. After obtaining the crystal structure of cyclopentyllithium, we focused on the solution structure of cyclopentyllithium because most of the reactions are conducted in solution. The solution-state characterization of cyclopentyllithium was carried out by applying various one- and two-dimensional NMR techniques on a solution of the crystal dissolved in toluene-d_8. The sample
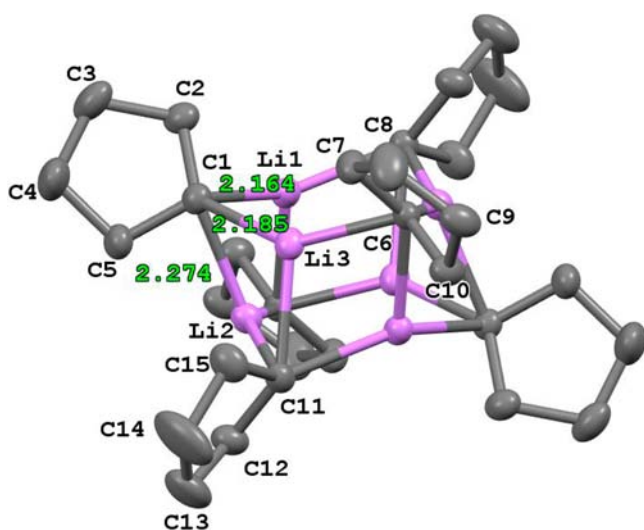
Figure 1. Crystal structure of hexameric cyclopentyllithium. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity. Crystallographic asymmetric unit atoms are labeled and C(1)−Li interatomic distances displayed.

was prepared by dissolving dry crystals of cyclopentyllithium that had been washed using anhydrous pentane twice in toluene-d_8. This solvent combination is unreactive with alkyllithium reagents in the absence of a coordinating ligand such as THF or N,N,N',N'-tetramethylethylenediamine (TMEDA) at room temperature.[10]

We first examined the ^{1}H NMR of cyclopentyllithium in toluene-d_8. The proton NMR shows two separate peaks in the methine region of cyclopentyllithium. It is believed that the two peaks originated from two different aggregates. To characterize the peaks, a variable-temperature NMR study with 1-dodecene (DDE) as internal reference was carried out, and the result is shown in Figure 2. When the temperature increases from −10 to −25 °C, the resonance at −0.77 ppm decreases significantly in intensity as the resonance at −1.14 ppm increases. The concentration of the two aggregates is easily determined by comparing the integrations of internal standard and the methine signals.[10a] We assigned the resonance at −0.77 ppm as hexamer and −1.14 ppm as tetramer because the concentration of tetramer increases upon elevation of temperature in the equilibrium reaction 1 depicted in Scheme 1. We conducted a dilution experiment at 15 °C (Figure 3) to verify our assignment, and this result is summarized in Table 1.

These results support our assignment of the resonances, because the calculated equilibrium constants are very similar according to the K given in Table 1. We then determined the enthalpy (ΔH) and entropy (ΔS) of the equilibrium of reaction 1 (Scheme 1) by a van't Hoff plot (Figure 4). The concentrations and equilibrium constants of reaction 1 (Scheme 1) at different temperatures were determined by variable-temperature ^{1}H NMR with 1-dodecene as internal reference, and the results are shown in Table 2. The van't Hoff plot has an excellent correlation ($R^2 > 0.99$). The enthalpy and entropy are calculated to be 38.2 kJ mol^{-1} and 99.7 J mol^{-1} K^{-1}, respectively. Comparison of the thermodynamic data for cyclopentyllithium with those of *sec*-butyllithium[11] reveals that the ΔH of *sec*-butyllithium is 64.8 kJ mol^{-1} or 1.7 times higher than that of cyclopentyllithium, whereas ΔS of *sec*-butyllithium is 262 J mol^{-1} K^{-1} or 2.6 times that of the ΔS of cyclopentyllithium. This is consistent with the fact that the
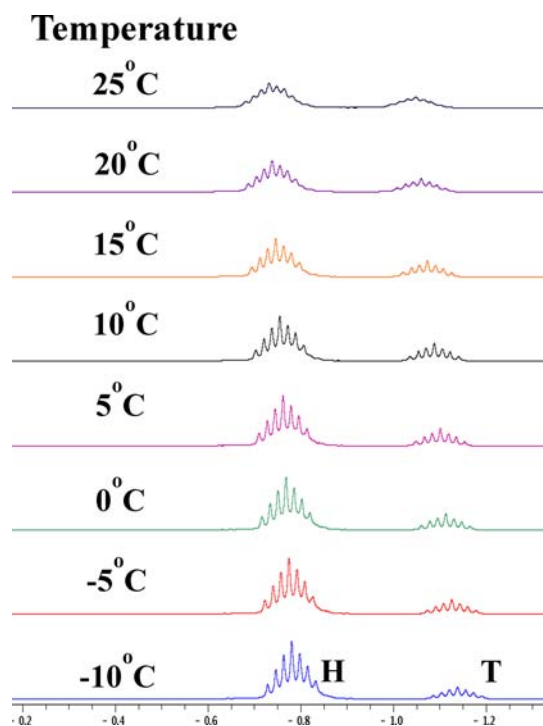
Figure 2. Variable-temperature ^{1}H NMR (400 MHz) spectra of 1.07 M c-PenLi in toluene-d_8. H represents the methine proton of c-PenLi hexamer (tt, J = 3.5 and 1.8 Hz.), T represents the methine tetramer proton (tt, J = 3.5 and 1.7 Hz).

Scheme 1. Equilibrium Reaction of the Hexameric and Tetrameric Complexes of c-PenLi
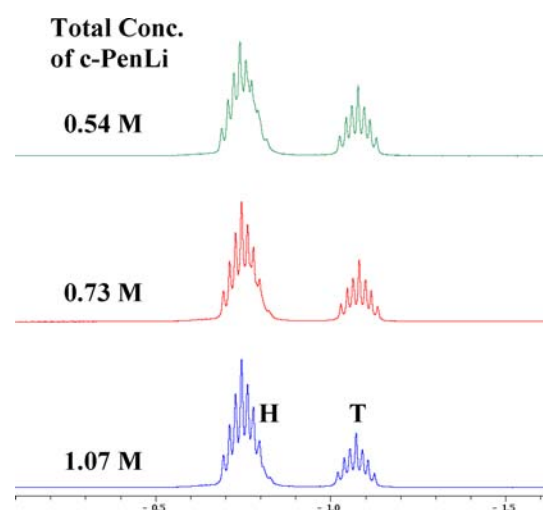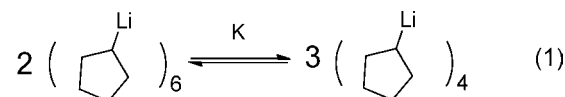
**Figure 3.** ^{1}H NMR (400 MHz) spectra of 1.07, 0.73, and 0.54 M c-PenLi in toluene-d_8 at 15° C. H represents the methine signal of c-PenLi hexamer, and T represents the signal of tetramer.

hexamer is the major species in cyclopentyllithium toluene solution, whereas tetramer is the major species for *sec*-butyllithium at room temperature.

A series of ^{1}H and ^{13}C NMR experiments including ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC were conducted

Table 1. Concentrations of Cyclopentyllithium (c-PenLi) Complexes and the Equilibrium Constant (K) at 15° C in Toluene-d_8

| concn of c-PenLi (M)		$K = \dfrac{(C_2/4)^3}{(C_1/6)^2}$
at −0.77 ppm, C_1	at −1.14 ppm, C_2	
0.798	0.272	0.0178
0.529	0.203	0.016
0.381	0.164	0.0170
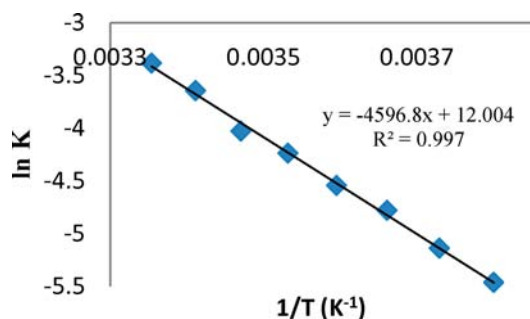
Figure 4. The van't Hoff plot of reaction 1 (Scheme 1).

for the sake of ^{1}H and ^{13}C signal assignment. We identified the resonances of methylene protons on carbons 2, 3, 4, and 5 using COSY, and the carbon signals were then assigned using HSQC NMR. The results are summarized in Table 3. We then carried out diffusion-ordered NMR spectroscopy (DOSY) and diffusion coefficient−formula weight (D−FW) correlation analyses to evaluate the formula weight of the aggregates. We applied DOSY NMR with internal references for the determination of formula weights of reactive complexes by D−FW correlation analysis. The formula weight of an unknown complex is deduced by its diffusion coefficient through the linear regression plot of the logarithms of NMR-determined diffusion coefficients against the known formula weights of the references.[12] Benzene (BEN, 78.11 g mol^{-1}), cyclooctene (COE, 110.2 g mol^{-1}), 1-tetradecene (TDE, 196.4 g mol^{-1}), and squalene (SQU, 410.7 g mol^{-1}) were used as internal references.

The resonances of methylene protons of c-PenLi from 1.0 to 2.5 ppm overlapped with those from the internal references; thus, distinct peaks from the methine protons were selected for our D−FW analysis (Figure 5).

The correlation between log FW and log D of the linear regression is very high ($r^2 > 0.99$), and the predicted formula

Table 3. ^{1}H and ^{13}C Signal Assignments of Hexameric and Tetrameric c-PenLi in Toluene-d_8

carbon atom	^{13}C (ppm)	^{1}H (ppm)
1	26.3	−0.78
2	34.7	1.09, 2.00
3	28.7	1.52, 1.76
4	21.8	−1.16
5	34.7	0.87, 1.93
6	28.8	1.79, 1.57
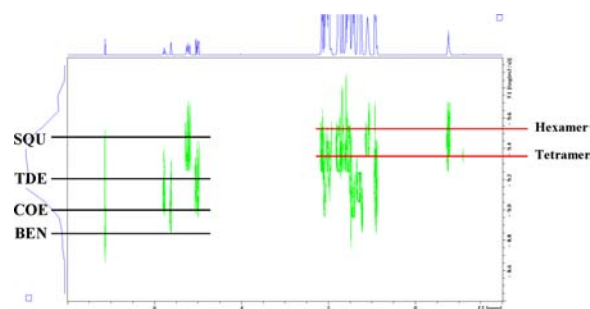
Figure 5. ^{1}H DOSY of c-PenLi toluene-d_8 solution at −25 °C.

weight for the resonance at −0.77 ppm is 443.5 g mol^{-1}, which is very close to the formula weight of the hexameric c-PenLi (456.4 g mol^{-1}, 2.8% difference). The predicted formula weight for the resonance at −1.14 ppm is 309.1 g mol^{-1}, which is only 1.6% different from the formula weight (304.3 g mol^{-1}) of the tetrameric c-PenLi (Figure 6, Table 4). Therefore, our DOSY result is consistent with the equilibrium reaction 1 (Scheme 1) of c-PenLi in toluene-d_8 and our hexamer−tetramer peak assignments.

Part II. Characterization of Cyclopentyllithium/THF Complex in Solid and Solution States. Cyclopentyllithium/ THF complex was easily crystallized in pentane. It exists as tetramer (c-PenLi)$_4$(THF)$_4$ in the solid state. Solution-state characterization of the complex dissolved in toluene-d_8 at low temperature reveals that tetrasolvated tetramer (c-PenLi)$_4$(THF)$_4$ is also the dominant species in solution.

Crystal Structure of Cyclopentyllithium/THF Complex. Cyclopentyllithium/THF crystals suitable for X-ray diffraction are easily grown from pentane solution. After the addition of THF to the pentane solution of c-PenLi, the solution is stored

Table 2. Concentrations of Different Cyclopentyllithium Complexes as a Function of Temperature in Toluene-d_8

T (°C)	$1/T$ (×10^{-3} K^{-1})	concn of c-PenLi^a (M)		K (×10^{-3} M)	ln K
		at −0.77 ppm, C_1	at −1.14 ppm, C_2		
−10.0	3.80	0.870	0.179	4.24	−5.46
−5.0	3.73	0.857	0.198	5.86	−5.14
0.0	3.66	0.848	0.221	8.39	−4.78
5.0	3.60	0.826	0.235	10.6	−4.54
10.0	3.53	0.812	0.257	14.5	−4.24
15.0	3.47	0.798	0.272	17.8	−4.03
20.0	3.41	0.793	0.308	26.1	−3.64
25.0	3.35	0.763	0.328	33.9	−3.38

^{a}The concentration was expressed as monomer units.
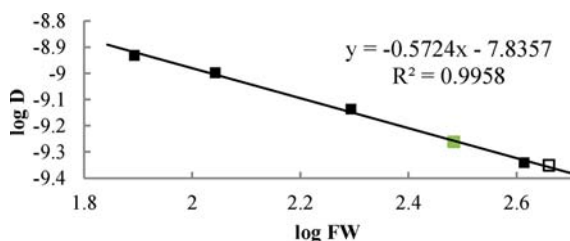
Figure 6. *D*−FW analysis of ^{1}H DOSY data. Internal references are shown as black squares, the tetrameric c-PenLi is shown as the green square, and the hexameric c-PenLi is shown as the unfilled square.

Table 4. *D*−FW Analysis of ^{1}H DOSY Data

entry	compd	FW (g mol^{-1})	$10^{-10}D$ (m^2/s)	predicted FW (g mol^{-1})	% error
1	BEN	78.11	11.73	81.84	−4.8
2	COE	110.2	10.07	106.8	3.1
3	TDE	196.4	7.311	186.9	4.8
4	SQU	410.7	4.569	424.9	−3.5
5	c-PenLi^a	456.4^a	4.458	443.5	2.8
6	c-PenLi^b	304.3^b	5.482	309.1	−1.6

^{a}The formula weight of hexameric c-PenLi complex is 456.4 g mol^{-1}. ^{b}The formula weight of tetrameric c-PenLi complex is 304.3 g mol^{-1}.

at −20 °C for 2 h, and colorless crystals are obtained. These crystals survive uncontaminated for a few hours, and the solution turns from colorless to yellow. We presume that this results from decomposition of THF by c-PenLi. X-ray diffraction analysis of the c-PenLi/THF crystal indicates a tetrameric c-PenLi aggregate with all lithium atoms coordinated to THF (Figure 7). Until now, only three crystal structures of
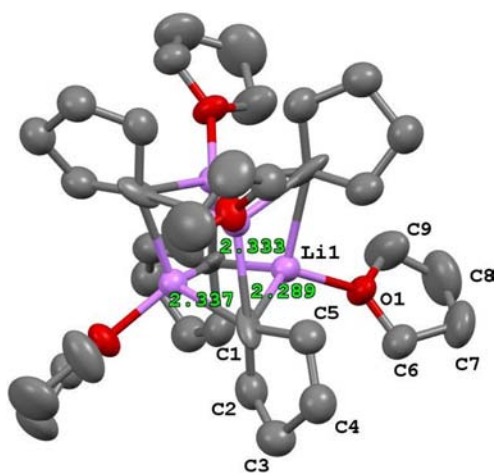

Figure 7. Crystal structure of tetrameric cyclopentyllithium/THF complex. Thermal ellipsoid plot shown at the 50% probability level. Hydrogen atoms have been omitted for clarity. Crystallographic asymmetric unit atoms are labeled and C(1)−Li interatomic distances displayed.

primary alkyllithium/THF complexes have been reported, and they are also tetrasolvated tetramers with each of the four lithium atoms coordinated to THF.[6,7] To the best of our knowledge, this is the first crystal structure of a secondary alkyllithium solvated by THF.

Characterization of Cyclopentyllithium/THF Complex in Solution. Because it is important to understand the solution structure of cyclopentyllithium/THF complex, we conducted a

series of NMR experiments to characterize the complex. The sample was prepared by dissolving the crystal of c-PenLi/THF complex into toluene-d_8 at −78 °C. All experiments were carried out below −30 °C to prevent significant reaction of c-PenLi with THF or toluene.

Unlike the unsolvated c-PenLi toluene solution, there is only one major peak in the methine region of c-PenLi for the THF solvated c-PenLi solution. To verify that only one dominant species exists for the THF solvate, we performed a low-temperature ^{6}Li NMR study on the c-PenLi/THF complex in which the lithium atoms are of natural abundance (Figure 8). The ^{6}Li spectra show one dominant peak and a small minor peak for the sample through −30 to −90 °C.
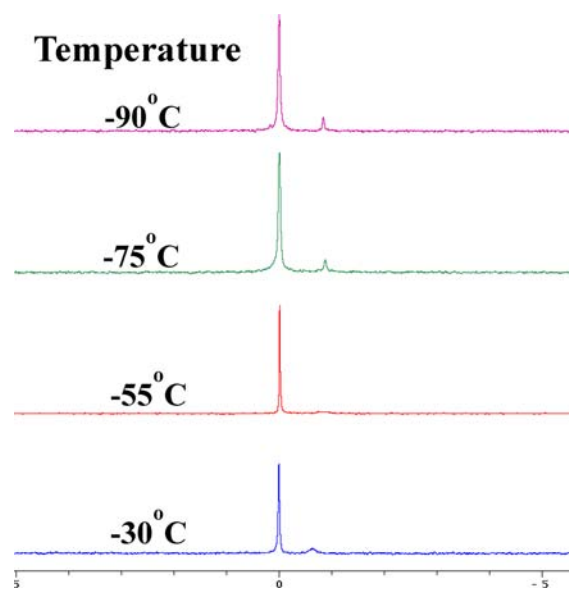

Figure 8. Variable-temperature ^{6}Li NMR spectra of naturally abundant c-PenLi/THF complex in toluene-d_8.

We again carried out a series of ^{1}H and ^{13}C NMR experiments to assign the ^{1}H and ^{13}C signals, including ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC. The signals of methylene protons on carbons 2 and 3 were first identified from COSY spectra, and the carbon resonances followed from HSQC spectra. The results are summarized in Table 5.

Table 5. ^{1}H and ^{13}C Signal Assignments of c-PenLi Solvated by THF in Toluene-d_8

carbon atom	^{13}C (ppm)	^{1}H (ppm)
1	23.8	−0.62
2	35.9	1.48, 2.29
3	29.4	1.66, 2.01
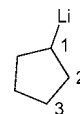
Diffusion-ordered NMR spectroscopy and *D*−FW correlation analysis were also performed to determine the formula weight of the c-PenLi/THF complex. Benzene, cyclooctene, 1-tetradecene, and squalene were used as internal references in this ^{1}H DOSY experiment, and the distinct peak from the methine proton of the c-PenLi/THF complex was selected for

our D–FW analysis because of the overlap of resonances from the internal references with the complex (Figure 9).
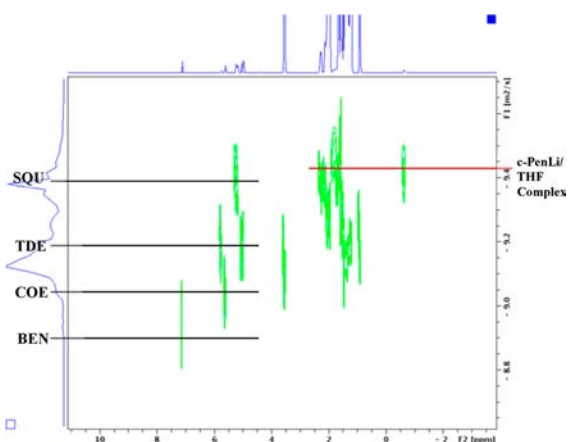
Figure 9. ^{1}H DOSY of c-PenLi/THF complex in toluene-d_8 solution at −35 °C.

The correlation of the linear regression is high ($r^2 = 0.99$), and the predicted formula weight from the c-PenLi methine resonance is 538.4 g mol^{-1}, which is 9.2% different from 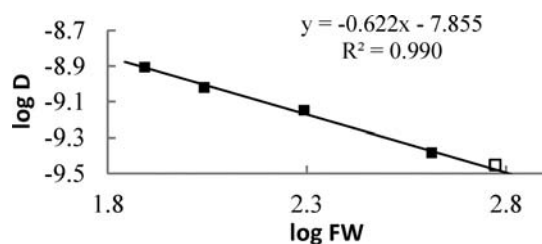the formula weight 592.7 g mol^{-1} of complex (c-PenLi)$_4$(THF)$_4$ (Figure 10, Table 6). The predicted formula weight is within

$$y = -0.622x - 7.855$$
$$R^2 = 0.990$$

Figure 10. D–FW analysis of ^{1}H DOSY data of c-PenLi/THF complex in toluene-d_8 solution at −35 °C. Internal references are shown as solid squares and the c-PenLi/THF complex is shown as an open square.

Table 6. D–FW Analysis of ^{1}H DOSY Data

entry	compd	FW (g mol^{-1})	$10^{-10}D$ (m^2/s)	predicted FW (g mol^{-1})	% error
1	BEN	78.11	12.41	77.33	1.0
2	COE	110.2	9.54	116.1	−5.3
3	TDE	196.4	7.10	183.1	6.8
4	SQU	410.7	4.14	422.4	−2.8
5	c-PenLi[a]	592.7[a]	3.54	539.6	9.2

[a]The formula weight of (c-PenLi)$_4$(THF)$_4$ complex is 592.7 g mol^{-1}.

the typical 10% error range for the D–FW analysis.[11] However, lowering of the predicted formula weight may also result from the influence of a small amount of dimer because we also observe a small, unassigned peak in the ^{6}Li NMR. Moreover, it is known that n-butyllithium exists as dimer and tetramer in THF solution;[13] therefore, it would not be surprising if a small amount of dimer is present in the c-PenLi/THF toluene-d_8 solution. Nevertheless, it is evident that the solid-state structure (c-PenLi)$_4$(THF)$_4$ is the dominant species in solution.

■ CONCLUSION

Cyclopentyllithium was easily crystallized in hydrocarbon solvent. This crystallization conveniently provides a process to obtain highly pure secondary alkyllithium reagent suitable for solution-state characterization and also for synthetic applications. X-ray diffraction reveals the hexameric nature of the cyclopentyllithium, whereas it exists as both a tetramer and a hexamer in hydrocarbon solvents. Moreover, cyclopentyllithium/tetrahydrofuran complex crystallizes readily from pentane at −20 °C, and the crystal structure is a tetrameric c-PenLi aggregate, with each lithium atom coordinated to THF forming the tetrasolvated, tetrameric aggregate (c-PenLi)$_4$(THF)$_4$. This same (c-PenLi)$_4$(THF)$_4$ tetramer is also the dominant species in solution.

The characterization of cyclopentyllithium in both solid and solution furthers our understanding of secondary alkyllithium reagents. We are currently conducting additional experiments to access the mechanism and reactivity of cyclopentyllithium by comparing it with isopropyllithium and *sec*-butyllithium.

■ EXPERIMENTAL SECTION

Procedures for NMR Experiments. Samples were transferred into NMR tubes. The NMR tubes were previously dried, evacuated in vacuo, filled with argon, and closed with rubber septa and Parafilm. ^{1}H chemical shifts were referenced to toluene-d_8 at 7.09 ppm, and ^{13}C chemical shifts were referenced to toluene-d_8 at 137.86 ppm. All NMR experiments were acquired using a 400 MHz spectrometer equipped with a z-axis gradient amplifier and an ATMA BBO probe with a z-axis gradient coil. Maximum gradient strength was 0.214 T/m. ^{1}H DOSY was performed using the standard dstebpgp3s program, employing a double-stimulated echo sequence, bipolar gradient pulses for diffusion, and three spoil gradients. Diffusion time was 200 ms, and the rectangular gradient pulse duration was 1200 μs. Gradient recovery delays were 200 μs. Individual rows of the quasi-2-D diffusion databases were phased and baseline corrected. Actual diffusion coefficients used for D–FW analysis were obtained with commercial software using the T1/T2 analysis module.

The cyclopentyllithium (c-PenLi) sample was prepared by dissolving dry crystals in toluene-d_8. The crystals were kept at −78 °C in a cold bath immediately after removing from a −20 °C freezer, the solvent was removed by syringe, and the crystals were washed twice with anhydrous pentane. After the removal of solution by syringe, the crystals were kept in a dry ice−acetonitrile bath and evacuated for 1 h. Toluene-d_8 was then added to the crystals under an argon atmosphere. The solution was allowed to stir at −42 °C for 20 min before syringing into a septum-capped NMR tube.

The cyclopentyllithium/THF sample was prepared by dissolving dry crystals in toluene-d_8 or by adding anhydrous tetrahydrofuran into a toluene-d_8 solution of cyclopentyllithium. The crystals were kept at −78 °C in a cold bath immediately after removing from a −20 °C freezer, the solvent was removed by syringe, and the crystals were washed with anhydrous pentane. After the removal of solution by syringe, the crystals were then kept at −78 °C and evacuated for 20 min. Toluene-d_8 (0.6 mL) was then added to the crystals under argon atmosphere. The resulting solution was transferred into a capped NMR tube via syringe at −78 °C. Alternatively, tetrahydrofuran was added via syringe into a sealed NMR tube of cyclopentyllithium toluene-d_8 at −78 °C. After the addition, the NMR tube was shaken vigorously at −78 °C before the signal acquisition.

For the variable-temperature experiments used to determine equilibrium constant and thermodynamic data, 51.1 mg of 1-dodecene was added via syringe to 0.650 mL of cyclopentyllithium toluene-d_8 solution to accurately measure the concentration of the cyclopentyllithium toluene-d_8 solution.

The internal references (in a ratio of 1:3:3:1 for BEN, COE, TDE, and SQU, respectively) were introduced into the NMR tube and

monitored by ^{1}H NMR. The titration was stopped when the peak intensity of benzene was similar to the methine peak of c-PenLi.

Synthesis of Cyclopentyllithium.[14] About 1.00 g (144 mmol) of finely cut Li metal was placed into a flame-dried flask with a condenser attached that was previously flushed with argon. The condenser was fitted with a serum septum and sealed with parafilm. The metal was washed by adding 10 mL of dry pentane to the flask via syringe. The flask was placed in an ultrasound bath for 15 min. Pentane was then removed via syringe. This was repeated until the washings were clear, with no white solid suspended in the wash (three times). Dry cyclohexane or heptane (10 mL) was added to the flask, and the flask was placed in an oil bath at 50 °C with stirring. A drop of methyl *tert*-butyl ether was added to 6.33 g (60.5 mmol) of chlorocyclopentane, and the resulting solution was added via syringe to the hot lithium metal cyclohexane or heptane mixture over a period of 2.5 h using a syringe pump. After the addition of chlorocyclopentane, the mixture was stirred overnight at room temperature, after which a purple slurry was obtained. The suspension was transferred via syringe to a clean, flame-dried vial flushed with argon and fitted with a serum septum. The vial was centrifuged until the solid was separated. The supernatant was transferred to a second identical vial and centrifuged again. The supernatant was transferred to a third identical vial. This cyclo-pentyllithium solution in cyclohexane or heptane was titrated using 2,2-diphenylacetic acid in tetrahydrofuran and found to be 2.0 and 1.4 M for the cyclohexane solution and heptane solution respectively.

Crystallization of Cyclopentyllithium. Cyclopentyllithium was easily crystallized from hydrocarbons by storing freshly made cyclopentyllithium cyclohexane solution or heptane solution at −20 °C overnight. A significant amount of colorless cyclopentyllithium crystals are obtained. XRD quality crystals are obtained directly from the heptane solution of cyclopentyllithium. Alternatively, the crystals were redissolved in toluene and the solution was stored at −20 °C for a few days before the appearance of colorless cyclopentyllithium crystals.

Crystallization of Cyclopentyllithium Tetrahydrofuran Adduct. To a 0.2 mL cyclopentyllithium heptane solution in a flame-dried vial under argon atmosphere at −20 °C was added 2 mL of anhydrous pentane. After 5 min, 0.1 mL of THF was added to the solution. The solution was shaken vigorously at −20 °C and stored at −20 °C. Colorless XRD quality crystals appeared after 2 h.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR and crystallographic data (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org. CCDC ⟨944702⟩ and ⟨944703⟩ contain complete crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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